

Prevalence and Predictors of Herbal Medication Use in Veterans with Chronic Hepatitis C

Uzma Siddiqui, MD, Elizabeth H. Weinshel, MD, FACG, and Edmund J. Bini, MD, MPH

Objective: Herbal therapies are used by a substantial proportion of persons in the United States, and use of these supplements may be even higher in those with chronic liver disease. The aims of this study were to prospectively determine the proportion of US veterans with chronic hepatitis C that are currently taking vitamins and herbal medications and to evaluate factors associated with use of herbal preparations.

Methods: Patients with hepatitis C who were seen in the gastroenterology, infectious disease, and primary care clinics at the VA New York Harbor Healthcare System were invited to participate in this prospective study. For comparison, healthy patients without hepatitis C were enrolled from the primary care clinics at the same medical center. Patients were interviewed by trained research coordinators who obtained detailed demographic and clinical data, as well as information on the use of antioxidants (vitamin C and E), multivitamins, and herbal medications.

Results: Use of vitamin C (34.8% vs. 19.6%, $P < 0.001$), vitamin E (25.8% vs. 13.2%, $P < 0.001$), multivitamins (43.6% vs. 28.0%, $P < 0.001$), and herbal therapies (21.0% vs. 10.4%, $P < 0.001$) was significantly higher in the 500 patients with hepatitis C compared with the 250 healthy controls. The most common herbal medications taken by hepatitis C patients were milk thistle (12.2%), ginseng (4.6%), and echinacea (3.0%). After adjusting for age and gender, multivariate logistic regression identified 12 or more years of education (OR 2.7; 95% CI 1.6–4.3; $P < 0.001$) and annual income of at least \$20,000 (OR 2.0; 95% CI 1.3–3.2; $P = 0.004$) as the only significant predictors of herbal medication use in patients with hepatitis C.

Conclusions: The use of herbal preparations is prevalent among veterans with chronic hepatitis C, especially those with higher levels of education and higher incomes. Obtaining a detailed medical history and documentation of the use of these supplements is critical to determine the potential for herbal-drug interactions and hepatotoxicity.

Key Words: herbal medications, complementary and alternative medicine, hepatitis C, liver disease, silymarin

(*J Clin Gastroenterol* 2004;38:605–610)

Herbal medication use is common in the United States and has increased by 380% over the past decade.¹ A large survey of the US population showed that herbal therapies were used by 12.1% of people in the past 12 months.¹ However, other studies have shown that a much higher proportion (14.3%–56.0%) of patients in industrialized nations are taking herbal medications.^{2–7} Herbal therapies are frequently used by patients to treat various chronic diseases, including chronic liver and digestive diseases,^{1,8} and 1 study found that 21.1% of patients seen in 6 different liver clinics in the United States were taking herbal medications.⁹

Data from the Third National Health and Nutrition Examination Survey (NHANES III) indicates that approximately 3.9 million people (1.8% of the population) have been infected with hepatitis C in the United States, and an estimated 2.7 million people have chronic infection.¹⁰ This figure may underestimate the true prevalence of hepatitis C because the population surveyed was limited to civilian, non-institutionalized individuals. In contrast, the prevalence of hepatitis C in veterans (6.6% to 39.9%) seems to be much higher than in the general population.^{11–17} Despite the high proportion of US veterans that are infected with hepatitis C, the prevalence of herbal medication use in this population has not been well studied. Therefore, the aims of this study are to prospectively determine the proportion of US veterans with chronic hepatitis C that are currently taking vitamins and herbal medications and to evaluate factors associated with use of herbal preparations.

METHODS

Study Population

Patients with hepatitis C who were seen in the gastroenterology, infectious disease, and primary care clinics at the Veterans Affairs (VA) New York Harbor Healthcare System were invited to participate in this prospective study. Hepatitis C patients were included if both hepatitis C antibody and hepatitis C viral RNA were positive. Patients were excluded from

Received September 25, 2003; accepted January 5, 2004

From the Division of Gastroenterology, VA New York Harbor Healthcare System, and NYU School of Medicine, New York, NY.

This study was presented in part at the Annual Meeting of the American College of Gastroenterology, Seattle, WA, October 21, 2002 (*Am J Gastroenterol*. 2002;97:S98).

Reprints: Dr. Edmund J. Bini, VA New York Harbor Healthcare System, Division of Gastroenterology (111D), 423 East 23rd Street, New York, NY 10010 (e-mail: Edmund.Bini@med.va.gov).

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the study if they had comorbid medical or psychiatric diseases, coinfection with HIV or hepatitis B, or had other causes of chronic liver disease. For comparison, healthy hepatitis C antibody negative patients without any comorbid disease were enrolled from the primary care clinics at the same medical center. All patients provided written informed consent to participate, and the Institutional Review Board at our hospital approved this study.

Study Design

All patients were interviewed by trained research coordinators who obtained detailed demographic data, including age, gender, race, employment status, annual income, education, era of military service, and risk factors for hepatitis C. Detailed information on the current use of antioxidants (vitamin C and E), multivitamins, and herbal medications was obtained from each patient. In addition, we recorded laboratory tests and liver biopsy results in those with hepatitis C. Data were abstracted on standardized data collection sheets and entered into a spreadsheet for analysis.

Statistical Analysis

Continuous variables were compared using the Student *t* test or the Mann-Whitney *U* test as appropriate. Data are expressed as means \pm SD for those variables that were normally distributed, and medians and interquartile range (25th percentile to 75th percentile) for those with a non-Gaussian distribution. Categorical variables were compared using the χ^2 test with Yates correction or Fisher exact test.

Univariate logistic regression analyses were used to identify those variables that were significantly associated with herbal medication use in patients with hepatitis C. Subsequently, a multivariate logistic regression model was created involving all significant variables identified in the univariate analyses. The multivariate regression analysis could then assess the independent effect of each variable in the model adjusted for the effects of each of the other variables. For each variable that was an independent predictor of herbal medication use in the multivariate model, the odds ratio (OR) and 95% confidence interval (CI) were calculated. The Hosmer and Lemeshow test was used to test the goodness of fit for the final multivariate logistic regression model.¹⁸ Statistical analysis was performed using SPSS software version 11.5 for Windows (SPSS Inc., Chicago, Illinois) and a two-tailed *P* value of <0.05 was considered statistically significant.

RESULTS

Baseline Patient Characteristics

Baseline characteristics of the 500 patients with hepatitis C and the 250 healthy controls are shown in Table 1. The majority was male patients and the population was racially diverse. There were no significant differences between the 2 groups with regard to age, gender, race, education level, employment status, or annual income.

Prevalence of Vitamin and Herbal Medication Use

Among the 750 patients enrolled in this study, 223 individuals (29.7%; 95% CI 26.5% to 33.1%) were currently tak-

TABLE 1. Baseline Patient Characteristics

	HCV Infected Patients (n = 500)	Healthy Controls (n = 250)	P-value
Age	51.7 \pm 8.5	51.6 \pm 11.4	0.93
Male	486 (97.2%)	241 (96.4%)	0.55
Race			0.37
African American	190 (38.0%)	89 (35.6%)	
White	173 (34.6%)	94 (37.6%)	
Hispanic	131 (26.2%)	60 (24.0%)	
Other	6 (1.2%)	7 (2.8%)	
Currently employed	233 (46.6%)	126 (50.4%)	0.33
Education, years	11.3 \pm 2.4	11.4 \pm 2.5	0.65
Annual income, median (IQR)	\$17,500 (\$12,650–\$22,100)	\$17,560 (\$13,450–\$22,000)	0.80
Era of military service			0.67
World War II	29 (5.8%)	20 (8.0%)	
Korean War era	39 (7.8%)	19 (7.6%)	
Vietnam War era	293 (58.6%)	147 (58.8%)	
Other	139 (27.8%)	64 (25.6%)	

ing vitamin C, 162 (21.6%; 95% CI 18.7% to 24.7%) were taking vitamin E, 288 (38.4%; 95% CI 34.9% to 42.0%) were taking multivitamins, and 131 (17.5%; 95% CI 14.8% to 20.3%) were taking 1 or more herbal medications.

Current use of vitamin C (34.8% vs. 19.6%; OR 2.2; 95% CI, 1.5–3.1; $P < 0.001$), vitamin E (25.8% vs. 13.2%; OR 2.3; 95% CI, 1.5–3.5; $P < 0.001$), multivitamins (43.6% vs. 28.0%; OR 2.0; 95% CI, 1.4–2.8; $P < 0.001$), and herbal medications (21.0% vs. 10.4%; OR 2.3; 95% CI, 1.4–3.6; $P < 0.001$) were significantly higher in the patients with hepatitis C compared with healthy controls (Fig. 1). In addition, patients with hepatitis C were significantly more likely to be taking more than one herbal medication compared with healthy controls (11.6% vs. 5.6%; OR 2.2; 95% CI, 1.2–4.0; $P = 0.009$).

A comparison of the specific types of herbal medications used by patients with hepatitis C and healthy controls is shown in Table 2. The most common herbal medications taken by hepatitis C-infected patients were milk thistle (12.2%), ginseng (4.6%), and echinacea (3.0%) and the most common herbal medications used by healthy controls were ginseng (2.8%), echinacea (2.8%), and milk thistle (2.4%).

Predictors of Herbal Medication Use in Hepatitis C-Infected Patients

Among the 500 patients with hepatitis C, a comparison of patients who used herbal medications and those who did not was performed. Univariate analysis demonstrated that 12 or more years of education (68.6% vs. 39.2%; OR 3.4; 95% CI 2.1–5.3; $P < 0.001$) and an annual income of at least \$20,000 (57.1% vs. 32.2%; OR 2.8; 95% CI 1.8–4.4; $P < 0.001$) were

significantly associated with herbal medication use in hepatitis C-infected patients. There were no significant differences between hepatitis C-infected patients who used herbal medications and those that did not with regard to age, gender, race, use of alcohol, smoking, risk factors for hepatitis C infection, proportion referred to the gastroenterology service, fibrosis stage on liver biopsy, hemoglobin, AST, ALT, total bilirubin, alkaline phosphatase, albumin, prothrombin time, or creatinine levels.

After adjusting for age and gender, multivariate logistic regression identified 12 or more years of education (OR 2.7; 95% CI 1.6–4.3; $P < 0.001$) and an annual income of at least \$20,000 (OR 2.0; 95% CI 1.3–3.2; $P = 0.004$) as the only significant predictors of herbal medication use in patients with hepatitis C. The Hosmer and Lemeshow goodness-of-fit test indicate that the final multivariate model fit the data well ($P = 0.74$).

DISCUSSION

Complementary and alternative medical (CAM) therapies include massage, acupuncture, chiropractic, yoga, prayer, meditation, hypnosis, aromatherapy, homeopathy, megavitamins, herbal medication use, and other practices.^{19,20} Previous studies have demonstrated that 49.6% of veterans use CAM therapies.¹⁹ Widespread CAM use has also been demonstrated in patients seen in liver clinics, with 1 study showing that 39.3% of patients in 6 geographically diverse liver clinics used some form of CAM at least once during the preceding month and 21.1% used herbal preparations.⁹ However, this study surveyed veterans and non-veterans and included pa-

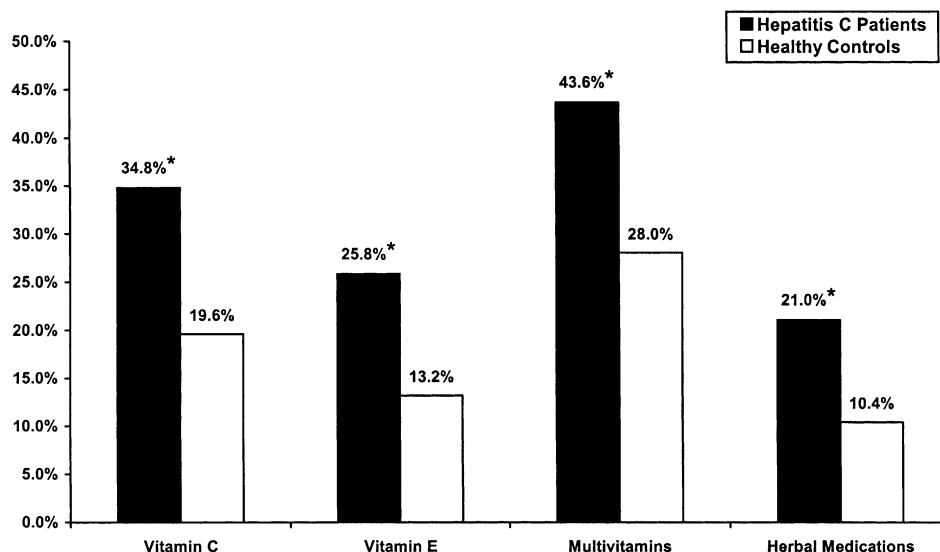


FIGURE 1. Prevalence of vitamin and herbal medication use among Hepatitis C-infected patients and healthy controls.

* $p < 0.001$ for comparison between hepatitis C patients and healthy controls

TABLE 2. Herbal Medications Used by Hepatitis C-infected Patients and Healthy Controls

Herbal Medications Used	HCV Infected Patients (n = 500)	Healthy Controls (n = 250)	P-value
Milk thistle	61 (12.2%)	6 (2.4%)	<0.001
Ginseng	23 (4.6%)	7 (2.8%)	0.24
Echinacea	15 (3.0%)	7 (2.8%)	0.88
St. John's Wort	13 (2.6%)	3 (1.2%)	0.29
Cat's claw	12 (2.4%)	3 (1.2%)	0.41
Saw palmetto	11 (2.2%)	4 (1.6%)	0.78
Ginkgo biloba	11 (2.2%)	4 (1.6%)	0.78
Mixed Chinese herbs	11 (2.2%)	4 (1.6%)	0.78
Garlic extract	10 (2.0%)	4 (1.6%)	0.78
Kava	8 (1.6%)	3 (1.2%)	0.76
Ephedra	5 (1.0%)	1 (0.4%)	0.67
Valerian	4 (0.8%)	1 (0.4%)	0.67
Glycyrrhizin	4 (0.8%)	2 (0.8%)	1.00
TJ-9	1 (0.2%)	1 (0.4%)	1.00

tients with various types of liver diseases. In contrast, our study included only veterans with hepatitis C and showed that these patients were significantly more likely to use vitamins and herbal medications than hepatitis C negative healthy controls. There are approximately 26 million veterans alive in the United States²¹ and the reported prevalence of hepatitis C in veterans is 6.6% to 39.9%.^{11–17} Therefore, there may be a very large number of hepatitis C-infected veterans in the United States who may be using vitamins and herbal preparations.

Milk thistle (silymarin) is the most commonly used herbal medication among patients with chronic liver disease^{9,20} and was also the most commonly used herbal therapy among our veterans with hepatitis C (milk thistle 12.2%, ginseng 4.6%, and echinacea 3.0%). Milk thistle was the 3rd most commonly used herbal supplement in our healthy controls, although the prevalence was significantly lower than those with hepatitis C (2.4% vs. 12.2%, $P < 0.001$).

The impetus for the use of milk thistle in liver disease stems from a few uncontrolled studies and case reports that demonstrate its efficacy in treating acute liver failure from Amanita mushroom poisoning.^{22,23} Subsequent randomized, placebo-controlled trials have shown that silymarin use results in improvement in ALT levels and liver histology in patients with alcoholic liver disease.²⁴ In a randomized, double-blind, placebo-controlled trial in 170 patients with alcoholic and non-alcoholic cirrhosis, Ferenci et al²⁵ showed that silymarin use was associated with an improved 4-year survival compared with placebo (58.0% vs. 39.0%, $P = 0.036$).

However, other studies have shown no benefit of silymarin in the treatment of chronic liver disease.^{8,26} The safety and efficacy of silymarin for the treatment of chronic hepatitis C remains to be determined.

In this study, we found that 12 or more years of education was an independent predictor of herbal medication use in our population. Higher education has also been shown to be a predictor of CAM use in other studies.^{2,9,19} Patients with a higher education may have greater access to computers and may be more likely to use the Internet than those with a lower education level. This hypothesis is supported by several studies that have shown that higher education was associated with increased use of the Internet for medical information.^{27–29} Furthermore, there are an abundance of Internet sites dedicated to herbal medications and their use in a variety of medical conditions, including liver diseases. Therefore, a more educated population may be more likely to use the Internet to find alternative treatments for their liver disease.

In addition to higher education, we also found that an annual income of \$20,000 or more was an independent predictor of herbal medication use in our patient population. This is consistent with previous observations that patients with higher incomes were more likely to use CAM therapies.^{2,9,19} In 1997, over \$27 billion was spent out-of-pocket on CAM therapies in the United States¹ and out-of-pocket expenses related to CAM use exceeded money spent for conventional healthcare in the United States, including hospitalizations and primary care visits.^{1,30} It has been estimated that as much as \$5.1 billion dollars is spent annually for herbal medications alone.¹ Due to the high cost of herbal medications and the fact that many insurance plans do not cover these expenses, it is not surprising that patients with higher incomes are more likely to use these therapies than those with lower incomes.

Many patients perceive herbal medications and vitamins to be safer and more effective than conventional medications.³¹ Herbal preparations, unlike conventional medications,

are not regulated by the Food and Drug Administration. This may result in lack of compound stability, mislabeling, and product contamination.³¹ Furthermore, the active ingredients in herbal medications are present in unverified concentrations.

It is clear that patients who use herbal medications are seeking alternative therapies, yet the majority of these individuals do not disclose this use to their physicians.^{2,4,32} Data from our medical center showed that 69.9% of veterans taking herbal supplements did not inform their physicians, whereas 89.0% reported that their physician did not inquire about herbal medication use.³³ Physicians must be aware that their patients may be taking herbal medications because of the possibility of side effects and interactions with traditional medical therapies. Use of herbal therapies is not without risk and a number of drug-herb interactions as well as adverse effects on the gastrointestinal tract and liver have been well-described.^{8,20} For example, increased bleeding may result from interactions between anticoagulants and ginkgo, ginseng, or St. John's wort,³¹ and chronic use of echinacea can increase hepatotoxicity in patients taking anabolic steroids, methotrexate, amiodarone, or ketoconazole.³⁴

Strengths of the present study include its prospective study design, the large number of hepatitis C patients surveyed, exclusion of patients with other comorbid diseases, and inclusion of hepatitis C negative healthy patients as a comparison group. However, there are several limitations to our study. Our population included predominantly male veterans who have a lower than average level of income and education. In addition, the subjects were enrolled at a single center in New York City. Therefore, our results may not be fully generalizable to other populations.

In conclusion, vitamin and herbal medication use is significantly more common among hepatitis C-infected veterans compared with healthy controls. In patients with chronic hepatitis C, education level and annual income were the most important determinants of herbal medication use. The high prevalence of herbal therapy use in this patient population emphasizes the importance of taking a detailed medication history and documentation of the use of these products to determine the potential for herbal-drug interactions. Further studies to evaluate the incidence of herbal medication-induced hepatotoxicity in this population are warranted.

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